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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/679,776	10/05/2000	Richard D. Granstein	2650/1F966-US1	8709

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No. 09/679,776	Applicant(s) GRANSTEIN, RICHARD D.	
	Examin r Q. Janice Li	Art Unit 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 23 April 2002 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☒ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-31*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 2. NOTE: Claim 24 has been amended to read on "a tumor antigen", which amendment has changed the scope of the claim, therefore, new issues need to be addressed such as Obviousness under 35 U.S.C. 103, thus a new search and considerations are required. The Examiner could not have foreseen that a tumor antigen is encompassed by the previous claim 24, because the applicant did not intend to claim the scope as it appears now, this could be shown by those claims which depend from claim 24. Further, the dependent claims of claim 24 are now broader in scope than the base claim from which they depend, because a tumor antigen does not embrace an allergen or a transplant antigen.

Continuation of 5. does NOT place the application in condition for allowance because:

Claims 1-31 stand rejected under 35 U.S.C. 112, first paragraph for reasons of record and the following.

The applicant asserts in Paper #11 that the specification, when considered with the teachings of the state of the art at the time of the invention, enables the full scope of the claimed invention both in the area of induction of protective immunity and induction of tolerance for the antigens encompassed by the scope of the claims. Applicants submitted 17 references to show the state of the art and the levels of the skill, and to support the arguments.

These arguments have been carefully considered but found not persuasive. This is because none of the references are directed to RNA vaccine or immunization; none of the references are directed to inducing tolerance to an autoantigen, an allergen, or a transplant antigen; and none of the references are directed to a successful RNA vaccination in humans.

It is not appropriate to use the references of DNA vaccination as the sole support for RNA vaccination, because, as cited in the first Office action and taught by Mitchell et al, the mode of action for DNA and RNA vaccines are simply different, they both have their advantages and drawbacks, a thorough comparison of the function of DNA and RNA vaccines has not been done or known in the art (see Section bridging pages 177-178). It is particularly true concerning the route of administration because the disadvantage of the RNA vaccine is the instability, that cellular RNA could be easily degraded by numerous factors. For example, Qui et al teach although using mRNA to transfer genetic information is highly desirable clinically, success in utilizing in vivo RNA delivery for transgene expression has been extremely limited, partially due to RNA instability and to the lack of an efficient intracellular delivery mechanism applicable to a wide variety of tissue or organ systems. Even though the applicant has shown that one type of tumor antigen survived the intravenous injection, it does not provide sufficient support commensurate with the scope of the claim to indicate that any antigen would survive the intravenous delivery and mount a sufficient immune response. If the applicant insists DNA vaccination is obvious over RNA vaccination, new grounds of rejection would be necessitated.

It is also not appropriate to use the references of DNA vaccine for tumor or influenza virus as evidence for RNA vaccination for any pathogen, allergen, autoantigen or transplantation antigen. This is because as stated in Papers #5 & #8, the mode of action of an immune response is distinct for different types of pathogens, allergens or autoantigens. For example, would the tolerance to HIV be induced if the HIV mRNA were to give to AIDS patients. For another example, tolerance to self-antigens is an essential feature of the immune system, and an autoimmune disease is caused by the loss of such essential feature in a host, wherein the mechanism of such loss is still largely unknown and most likely involves defects of the host immune system. Therefore, simply administering an autoantigen as an attempt to re-establish the feature of self-tolerance is unlikely to be successful and has not been shown otherwise in the instant specification. Thus, the specification fails to provide an enabling disclosure commensurate in scope with the claims.

In addition, the applicant submitted another Declaration under Rule 132 to indicate that the claimed invention is effective in reducing the rate of tumor growth in two mouse tumor models. However, as indicated in Paper #5 & #8, the skilled artisan, Mitchell et al, McCluskie et al, and Boucher et al have concluded that what shows effective in mouse is not predictable in humans.

For the reasons of record and those set forth above, the instant specification fails to meet the enablement requirement for the broad scope.

Claims 24 and 30 stand rejected under 35 U.S.C. 102(b) as being anticipated by Qiu et al (Gene Ther 1996;3:262-68) for the reason of record and set forth following.

Applicants argue that Qui et al does not disclose the claimed invention because the compositions of Qui et al do not meet the standards required for in vivo delivery into humans required by the present invention. This issue has been addressed in the final rejection that the art-known carrier composition used for gene gun delivery does not appear different in animal models and in humans. In the working example, the pharmaceutical carrier for the RNA is normal saline, which could be used in both humans and animals. Further, besides firefly luciferase, Qui et al also delivered human growth hormones and human alpha-1 antitrypsin to mice, which clearly indicate that the mouse study is set forth as feasibility study for humans, therefore, the formulation for mice should be applicable in humans. Thus, Qiu et al still anticipate the instant claims.

JAMES KETTER
PRIMARY EXAMINER